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Prophylaxis use among males with haemophilia B in the United States

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Abstract

Introduction—Prophylaxis is considered the optimal treatment for persons with moderate to severe haemophilia (factor activity between 1–5% of normal and <1% of normal respectively) in countries where safe factor concentrates are available and economically feasible. Historically, prophylactic treatment has not been well studied in the haemophilia B (HB) population due to difficulties in obtaining a sufficiently large sample.

Aim—This study examines the prevalence of prophylaxis use among a robust sample of persons with HB in the United States and its association with specific demographic and clinical characteristics.

Methods—Using data collected between 1998 and 2011 for the Centers for Disease Control and Prevention's Universal Data Collection project, we analysed data on 2428 males with moderate to severe HB aged 2–79 years who were seen at 135 federally funded haemophilia treatment centres.

Results—Prevalence of prophylactic treatment in our sample was 35% among children and youth (ages 2–19) and 14% among adults (age 20 and older). Increased HB prophylaxis use was significantly associated with younger age (<40 years), Hispanic ethnicity, severe disease and self-

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DISCLOSURES

The authors state that they have no interests that might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

M Ullman wrote the paper; QC Zhang designed the study and analysed the data; SD Grosse designed the study and edited the paper; M Recht provided clinical expertise and edited the paper; JM Soucie designed the study. All authors reviewed and revised progressive drafts of the manuscript and approved the final version.

infusion, while decreased use was associated with above-normal body mass index (BMI) in adults. Health care coverage was vital, although type of coverage did not appear to influence access.

Conclusions—Our analysis confirms previous reports of lower prevalence of prophylaxis use among individuals with HB compared to those with haemophilia A and adds to the body of knowledge regarding treatment patterns among a historically understudied population.

Keywords

BMI; ethnicity; haemophilia B; obesity; overweight; prophylaxis

1 | INTRODUCTION AND BACKGROUND

Prophylaxis, the regularly scheduled infusion of factor concentrate to prevent bleeding, is considered the optimal treatment for all persons with severe haemophilia.[1,2] By raising factor VIII (FVIII) or factor IX (FIX) activity levels above one percent of normal, prophylaxis reduces spontaneous bleeding and subsequent joint arthropathy, and is associated with improved physical and psychosocial outcomes.[3–6] Routine use of prophylaxis beginning early in life was pioneered in northern Europe in the 1950s; its effectiveness among individuals with severe haemophilia A (HA) was confirmed in two landmark randomized clinical trials published in 2007 (US) and 2011 (Italy).[7,8] Both studies demonstrated the ability of preventative therapy to reduce joint damage compared to factor administered after bleeding. The impact of the US study was evident in a 2010 survey of US haemophilia treatment centres (HTCs) in which 66% of severe HA patients received some form of prophylaxis, a 10% increase from 2008.[9]

Previous reports suggest that persons with HA are more likely than those with haemophilia B (HB) to use prophylaxis and have revealed variations in prophylaxis use among US HTCs.[9,10] Possible explanations for lower prophylaxis use in HB include the greater prevalence of mild and moderate HB patients compared to those with HA and a less severe clinical phenotype.[11,12] Few studies have focused exclusively on prophylaxis in HB because of the difficulty of obtaining a robust sample; therefore much of our knowledge regarding prophylaxis use is based on the HA population. The question of whether persons with severe HB should be placed on a prophylactic regimen as frequently as those with severe HA remains a subject of debate among haemophilia care providers.[13–18]

Using a large national sample, this study (i) examines the prevalence of prophylaxis use among individuals with moderate and severe HB and (ii) investigates the association of prophylaxis use with clinical and demographic factors similar to those previously reported in the HA population.

2 | METHODS

The Universal Data Collection (UDC) surveillance project was conducted by the CDC and 135 federally funded HTCs in the US to collect a uniform set of clinical outcomes data on persons who received comprehensive care at these centres. More than 18 000 males, representing 85% of persons with haemophilia receiving care at HTCs, were enrolled from

1998 to 2011.[10,11] From a study population of 3825 males aged 2–79 years diagnosed with HB, we excluded individuals with mild disease (n=943) and clinical or treatment characteristics having the potential to affect weight status or the ability to treat prophylactically, including a diagnosis of HIV or symptomatic liver disease (n=704); inhibitor titre ≥5 Bethesda units (n=21); and immune tolerance therapy at the time of the visit (n=6). Individuals using intermittent prophylaxis (prophylaxis not expected to continue for an indefinite period of time) were excluded (n=6), as were those with incomplete height and weight data at the time of the most recent UDC visit (n=112). The study sample includes 2428 persons with moderate or severe HB.

Demographic and clinical data were collected from consenting UDC participants by HTC staff members during UDC visits using standardized data collection instruments. The registration form (completed once at enrollment) recorded month and year of birth, gender, race/ethnicity, factor deficiency, diagnosis and baseline factor activity; the annual visit form (completed at subsequent visits) collected visit date, current height, weight, insurance coverage, home infusion status, person performing the infusion (self, family member or medical care provider) and treatment regimen (episodic or prophylaxis). Data from the most recent UDC visit were used in the analyses.

2.1 | Definition of variables

CDC guidelines, including gender-specific growth charts, were used to define categories of overweight and obesity based on measured height and weight. Above-normal body mass index (BMI) in adults was defined as BMI≥25.0; in children and youth 2–19 years, as BMI-for-age ≥95th percentile. Obesity was defined as BMI≥30 for adults and as BMI-for-age ≥97th percentile for those <20 years. Participants with baseline factor activity between 1–5% of normal levels were considered to have moderate haemophilia, and those with <1%, severe haemophilia.[1] Participants were grouped into five age categories: (i) 2–5 years; (ii) 6–11 years; (iii) 12–19 years; (iv) 20–39 years; and (v) 40 years or older. Treatment type was classified as episodic if the patient received products only in response to bleeding complications since the last annual clinic visit. Individuals were considered to be on a prophylactic regimen if they received treatment products on a regular schedule expected to continue indefinitely in order to prevent any and all bleeding. We examined four categories of insurance coverage: (i) no insurance; (ii) commercial insurance; (iii) publicly funded insurance (Medicaid, CHIP, Medicare, Tricare and state programmes for chronically ill/disabled persons); and (iv) all other forms of insurance. Persons with any form of commercial or public health care coverage were considered to have health insurance. For analysis of geographic variation, the sample was divided into four U.S. Census Bureau geographic regions: West, Midwest, Northeast and South. Racial/ethnic groups included non-Hispanic White, African-American (non-Hispanic black), Hispanic and Other.

2.2 | Statistical methods

We conducted descriptive and bivariate analyses followed by a series of multiple logistic regression models to assess the independent associations of prophylaxis use with demographic and clinical characteristics.

Percentages of age, race/ethnicity, health insurance status, BMI, severity, self-infusion status and geographic location were calculated to describe demographic and clinical characteristics. The prevalence of prophylaxis use for each level of these variables was calculated. Bivariate analyses with Pearson's chi-square tests were used to assess differences in prophylaxis use within subgroups.

Multiple logistic regression models were developed to examine whether race/ethnicity was associated with the likelihood of using prophylaxis, adjusting for all other variables. Analyses were conducted on the entire sample and then separately on adults (20 years and older) and non-adults (2–19 years) to show differences in prophylaxis use between age groups. Since first-degree interactions of age with BMI (P=.09) and with race/ethnicity (P=.18) were not significant, we reported the adjusted odds ratios, 95% confidence interval and P values from the main effect models.[19]

We then developed additional polynomial logistic regression models using age as a continuous variable to demonstrate the impact of advancing age on the probability of using prophylaxis among the four race/ethnicity subgroups. Figures based on these models illustrate the mean predicted probability of using prophylaxis with advancing age among the study population.

All statistical analyses were based on two-sided tests with a significance level of 0.05 and conducted using SAS 9.3 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Characteristics of the study population

Our sample included 2428 individuals with moderate or severe HB, aged 2–79 years (Table 1). Half (51%) were aged 2–19, the majority of the study population were (75%) non-Hispanic White and most individuals (90%) had either commercial or publicly funded health insurance. Nearly half (49%) had above-normal BMI; 23% were obese. Moderate was the most common haemophilic severity (56%). Nearly one-quarter (23%) of all teens aged 12–19 practiced self-infusion, as did more than half of adults (53%) (data not shown).

3.2 | Prevalence of prophylaxis use

Proportionate use of prophylaxis was greatest among 6–11-year olds (40%), followed by 2–5-year olds (35%) and teens 12–19 years (32%). Overall, prophylaxis was used by roughly one-third (35%) of those aged 2–19 years (Table 1). Individuals <20 years of age accounted for 73% of prophylaxis users. Among teens on a prophylactic regimen, 33% self-infused (data not shown).

Prophylaxis was used by less than one-fifth (14%) of all adults, and the proportion generally declined steadily with age, although Figure 1 reveals an increase in prophylaxis use among older individuals with severe HB aged 50–65 years. The proportion of younger adults (20–39 years) on prophylaxis (17%) was twice that among adults 40 and older (8%). However, among self-infusers, the proportion using prophylaxis remained constant despite increasing age (81% among ages 20–40; 80% among those 40 years and older [data not shown]).

Not surprisingly, prophylaxis was used more by persons with severe than moderate HB and by those with commercial or public insurance vs some other or no health insurance (Table 1). Prophylaxis use was most common among Hispanic males and least common among non-Hispanic Whites (Figure 1). Among adults, the ability to self-infuse appeared to increase prophylaxis use, while overweight and obesity appeared to decrease use. Geographic differences in prophylaxis use fell short of the significant level (P=.053), although the trend suggested highest use in the West and lowest use in the Midwest.

3.3 | Association of prophylaxis use with demographic and clinical characteristics

In a multivariate analysis that included all of the studied characteristics (Table 2), several factors were independently associated with prophylaxis use. Patient age was strongly associated with prophylaxis use; younger patient groups were much more likely to use this therapy than adults 40 years or older.

The association of prophylaxis use varied significantly among racial/ethnic groups (P<.001); Hispanic ethnicity was strongly associated with increased prophylaxis use [AOR= 1.9 (1.4–2.7), P≤.0002]. Surprisingly, children of Hispanic race/ethnicity were nearly twice as likely to use prophylaxis as non-Hispanic Whites.

Health insurance coverage was significantly associated with increased prophylaxis use [commercial insurance: AOR=6.1 (2.9–13.2), P≤.0001; publicly funded insurance: AOR=6.3 (2.9–13.7), P≤.0001]. Those with commercial or publicly funded health insurance were six times more likely to use prophylaxis than those with no health insurance. BMI tended to interact with age group (P=.09, results not reported). Decreased use of prophylaxis was associated with overweight [AOR 0.5 (0.4–0.8), P=.01] and obesity [AOR 0.6 (0.4–1.0), P=.04] among adults, but not among those <20 years. Severity was strongly associated with prophylaxis use: non-adults with severe haemophilia were nearly 10 times more likely to use prophylaxis than those with moderate disease [AOR=9.8 (7.2–13.2), P≤.0001], while adults with severe disease were six times more likely to treat prophylactically [AOR=5.9 (3.7–9.5), P≤.0001. Finally, self-infusion was significantly associated with increased prophylaxis use among adults [AOR=2.7 (1.7–4.2), P≤0.0001].

4 | DISCUSSION

Prophylaxis is associated with improved health and psychosocial outcomes but is costly. Factor concentrate accounts for most medical expenditures; a recent analysis found the median annual cost of factor for those with severe HA using prophylaxis to be $289 172, compared to $170 037 for episodic treatment.[20] An understanding of utilization patterns is needed to effectively balance health care outcomes and resource utilization, especially as new therapies, such as extended half-life factor products, are introduced.

Among our sample, 24.6% of those with HB used prophylaxis, compared with 47.2% of those in the UDC with HA using prophylaxis.[11] This difference is consistent with Canadian data in which 32% of those with severe HB used prophylaxis, compared to 69% of those with HA.[14]

Evidence that HB may be clinically less severe than HA, possibly due to a milder bleeding phenotype, includes less frequent bleeding in those with HB, lower rates of arthroplasty and lower factor usage.[12,13,15] The lower use of prophylaxis use among HB populations may be the result of less severe disease (due to more missense mutations), providers' use of established haemophilia treatment practices and customs, or a combination of these factors.[21]

4.1 | Health care coverage

Health care coverage appears essential for accessing prophylactic treatment, as reported by Baker et al.[22] The overall proportion of individuals with HB covered by some form of health care insurance was high (90%), but nearly twice as many adults (13%) as 2–19-year olds (7%) were uninsured. Because data were collected prior to implementation of the Affordable Care Act (ACA), some adults in our sample may have experienced greater barriers to prophylactic treatment than children and teens, as they were ineligible for Medicaid or Medicare coverage unless disabled. Additionally, lifetime limits on commercial insurance prior to the ACA may have restricted adults' use of prophylaxis. Our sample includes individuals from the first generation to live into older age, when muscle wasting, severe arthropathy, and comorbidities can warrant aggressive therapy. Increasing prophylaxis use among 50–65-year olds with severe HB across all races/ethnicities (Figure 1) may be related to older individuals' access to Medicare and thus prophylaxis.

Virtually all 2–19-year olds on prophylaxis were covered by some form of insurance (55% commercial insurance and 44% public insurance); only 1% had no coverage. Among adults using prophylaxis, 52% had commercial insurance, 43% had public insurance and 3% were uninsured. The fact that similar proportions of persons with publicly funded insurance (29%) and commercial insurance (26%) used prophylaxis suggests that insurance type is not a barrier to optimal care for persons treated at HTCs. Additional studies using socio-economic data would broaden our understanding of barriers to recommended haemophilia treatment among adults.

4.2 | Race and ethnicity

Our finding of significantly higher levels of prophylaxis use among Hispanic individuals compared to other racial/ethnic groups, provided they had insurance [AOR=1.9 (1.4, 2.7), P=.0002, Table 2], was unexpected. One possible explanation is the differing proportion of individuals with severe disease: 38% of non-Hispanic Whites, compared to 65% of African-Americans and 65% of Hispanics. However, the larger proportion of those with severe haemophilia among minority groups does not explain the greater use of prophylaxis (among all ages) by Hispanics (47%) compared to African-Americans (30%), both of whom comprise a similar proportion of the overall sample population (10% and 9% respectively). Another explanation may be different prescribing patterns in states containing large proportions of African-American or Hispanic individuals; these patterns could be driven by more generous state funding for insurance programmes for persons with chronic illness or disability.

Disparity in prophylaxis use among racial/ethnic groups was observed in both public and commercial coverage groups. Among those aged 2–19 with public insurance (generally Medicaid or Children's Health Insurance Program (CHIP)), 63% of Hispanics used prophylaxis, compared to 36% of African-Americans and 29% of non-Hispanic Whites. Among those in the same age group covered through commercial insurance, 49% of Hispanics used prophylaxis, compared to 38% of African-Americans and 35% of non-Hispanic whites. This finding indicates that HTCs provide access to optimal therapy across sociodemographic groups. We observed no significant association with prophylaxis among Hispanic adults, possibly because of the low prevalence of use among the overall adult population (14%), and insufficient sample size (n=67), which may reflect the fact that some adult Hispanics are unable to access insurance coverage (and therefore prophylaxis) due to lack of legal US residency.

4.3 | Increased BMI

Although obesity was significantly associated with lower prophylaxis use only among adults, young persons were disproportionally affected by obesity (19% of 2–11-year olds and 16% of teens, compared to 11% of adults). Among 2–11-year olds, obesity was more prevalent than overweight; among those with obesity, 14% had morbid obesity. National Health and Nutrition Examination Survey data collected in 2009–2010 indicate that although the prevalence of obesity among the general U.S. population has stabilized among most age groups, it continues to rise among male adolescents.[23]

An obesity prevalence approaching 20% among those most likely to use prophylaxis (2–11-year olds) has significant economic implications. Prophylactic regimens can use up to three times more factor concentrate than episodic treatment.[24,25] Dosing is based on actual, not ideal, body weight; consequently, a prophylactic regimen for an obese or overweight child is more costly than for one of normal weight. Using patient data from one HTC, prophylactic factor costs for 19 overweight or obese 2–19-year olds with severe HA or HB not using a bypassing agent would cost over $1 million per year (ie roughly $50 000 per person on average) more than if they had a normal body weight, not taking into account 340B program subsidies.[26] In our sample, 163 overweight or obese 2–19-year olds were treated prophylactically, using an estimated $8 million dollars more in factor costs than if they were of normal weight. Public funds covered 29% of individuals using prophylaxis. In an era of constrained healthcare resources, monitoring the BMI of young males at risk for obesity and initiating preventive measures must become a priority for HTCs.

4.4 | Study limitations

Some limitations should be noted when interpreting our results. Data were collected prior to the introduction of extended half-life factor IX products; widespread adoption of these may alter future patterns of prophylaxis use by making prophylactic treatment more accessible for patients. Our sample was derived from volunteer participants receiving care through federally funded HTCs. The prevalence of HB in our study population (25%) is slightly higher than some published estimates, possibly due to the greater number of blood-borne virus-related deaths among persons with severe HA during the past 25 years.[27] We also note that the prevalence of individuals with severe HB (45%) is higher than that reported by a

Canadian survey of HTCs (32%).[14] Data collected for the UDC surveillance project were not confirmed with pharmacy or home care records. BMI does not distinguish between fat mass and fat-free mass; however, studies demonstrate that the association between BMI and body fat is strong among those with higher BMI levels.[28] Small sample size may be an issue in analyses of subgroups stratified simultaneously by numerous variables, such as Hispanic persons >40 years using prophylaxis.

5 | CONCLUSION

We found that (i) the overall prevalence of prophylaxis use among males with moderate and severe HB was 25% among individuals with moderate disease and 45% among those with severe disease; and (ii) age and severity are strongly associated with HB prophylaxis use. Prophylactic treatment was associated with young age: 6–11-year olds were the most likely to use prophylaxis, while adults 40 years and older were the least likely to do so. Prophylaxis was used by nearly six times as many individuals with severe disease as those with moderate haemophilia.

Health care coverage was vital: only eight individuals (3 aged 2–19 and 5 adults) without insurance used prophylaxis; type of coverage (public vs commercial) did not appear to influence access. Increased prophylaxis use was associated with younger age and Hispanic race/ethnicity, while above-normal BMI in adults was associated with decreased prophylaxis use. Future analyses directly comparing the use of prophylaxis among US HA and HB populations, racial/ethnic groups and geographic regions will increase our understanding of evolving haemophilia treatment patterns and implications for the allocation of haemophilia treatment resources.

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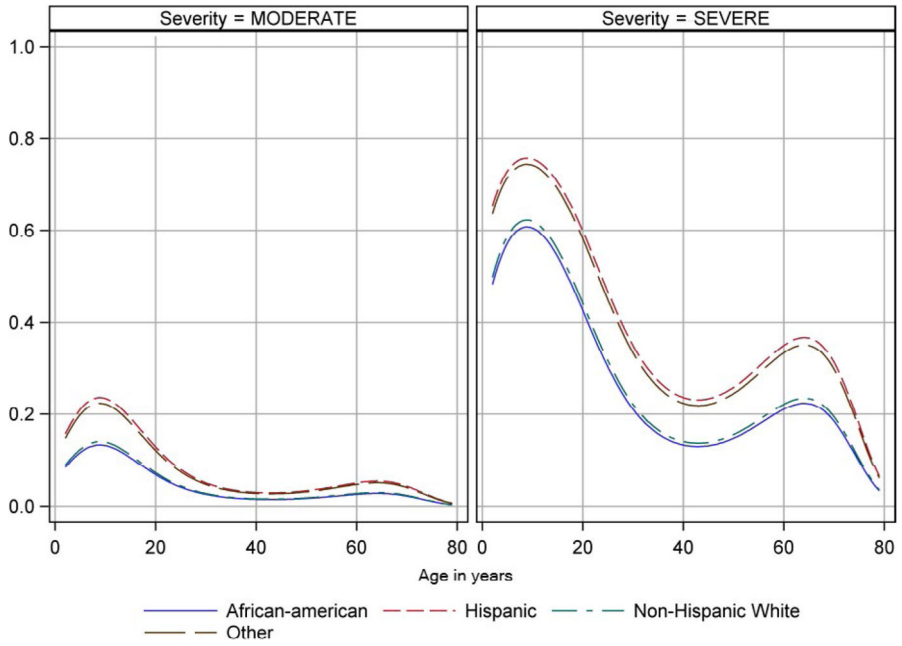

FIGURE 1.

Predicted probability of prophylaxis use in males with moderate to severe haemophilia B by race/ethnicity

TABLE 1

Prevalence of prophylaxis use by patient characteristics among males with moderate to severe haemophilia B

Characteristic	Total[a] N=2428, No. (%)	Prophylaxis use[b] N=598, No. (%)	Episodic treatment N=1830, No. (%)	*P* value[c]
Age				
All youth (2–19 y)	1246 (51)	437 (35)	809 (65)	<.0001
All adults (20+ y)	1182 (49)	161 (14)	1021 (86)	
2–5 y	240 (10)	84 (35)	156 (65)	<.0001
6–11 y	399 (16)	160 (40)	239 (60)	
12–19 y	607 (25)	193 (32)	414 (68)	
20–40 y	725 (30)	126 (17)	599 (83)	
40+ y	457 (19)	35 (8)	422 (92)	
Race/ethnicity				
Non-Hispanic White	1810 (75)	355 (20)	1455 (80)	<.0001
African-American	230 (9)	70 (30)	160 (70)	
Hispanic	241 (10)	114 (47)	127 (53)	
Other	147 (6)	59 (40)	88 (60)	
Health insurance				
Commercial	1269 (52)	326 (26)	943 (74)	<.0001
Publicly funded	888 (37)	261 (29)	627 (71)	
Other/unknown	31 (1)	3 (10)	28 (90)	
No insurance	240 (10)	8 (3)	232 (97)	
BMI status				
Normal weight or less	1233 (51)	352 (29)	881 (71)	<.0001
Overweight	640 (26)	128 (23)	427 (77)	
Obese	555 (23)	118 (18)	522 (82)	
Severity				
Moderate	1349 (56)	109 (8)	1240 (92)	<.0001
Severe	1079 (44)	489 (45)	590 (55)	
Self-infusion				
Yes	772 (32)	198 (26)	574 (74)	.45
No	1656 (68)	400 (24)	1256 (76)	
Census bureau regions[d]				
Midwest	877 (36)	146 (17)	731 (83)	<.0001
Northeast	494 (20)	133 (27)	361 (73)	

Characteristic	Total[a] N=2428, No. (%)	Prophylaxis use[b] N=598, No. (%)	Episodic treatment N=1830, No. (%)	*P* value[c]
South	590 (24)	162 (27)	428 (73)	
West	467 (19)	157 (34)	310 (66)	

[a] Distribution of demographic and clinical characteristics among males with Haemophilia B, row %.

[b] Prevalence of prophylaxis use, column %.

[c] *P* value calculated using Chi-squared test.

[d] Percentages in the total column sum to 99%; the remaining 1% is distributed nearly evenly among the four regional categories.

TABLE 2

Independent association of patient characteristics with prophylaxis use by age in males with moderate to severe haemophilia B (HB)

	All HB, 2–79 y (N=2428)		Non-adults, 2–19 y (N=1246)		Adults, 20–79 y (N=1182)	
Characteristic	**AOR (95% CI)[a]**	***P* value**	**AOR (95% CI)[a]**	***P* value**	**AOR (95% CI)[a]**	***P* value[a]**
Age						
2–5 y	8.6 (5.0, 14.7)	<.0001	1.1 (0.8, 1.7)	.55	–	–
6–11 y	14.6 (8.8, 24.0)	<.0001	1.9 (1.4, 2.7)	.0002	–	–
12–19 y	7.2 (4.6, 11.4)	<.0001	Ref.-	–	–	–
20–40 y	2.3 (1.5, 3.5)	.0002	–	–	2.1 (1.3, 3.3)	.001
40 y and older	Ref.	–	–	–	Ref.	–
Race/Ethnicity						
Non-Hispanic White	Ref.	–	Ref.	–	Ref.	–
African-American	0.9 (0.7, 1.4)	.78	0.7 (0.4, 1.1)	.10	1.7 (0.9, 3.0)	.09
Hispanic	1.9 (1.4, 2.7)	.0002	2.0 (1.3, 3.0)	.001	1.6 (0.8, 3.1)	.17
Other	1.9 (1.2, 2.9)	.003	1.3 (0.8, 2.3)	.29	3.3 (1.7, 6.4)	<.01
Health insurance						
No	Ref.	–	Ref.	–	Ref.	–
Commercial	6.1 (2.9, 13.2)	<.0001	11.4 (3.3, 39.2)	.0001	3.5 (1.3, 9.3)	.01
Publicly funded	6.3 (2.9, 13.7)	<.0001	11.0 (3.2, 38.1)	.0002	4.1 (1.5, 11.1)	.01
Other/Unknown	1.4 (0.3, 6.6)	.64	0.9 (0.1, 11.1)	.96	4.8 (0.6, 35.8)	.13
BMI Status						
Normal weight or less	Ref.	–	Ref.	–	Ref.	–

Characteristic	All HB, 2–79 y (N=2428)		Non-adults, 2–19 y (N=1246)		Adults, 20–79 y (N=1182)	
	AOR (95% CI)[a]	*P* value	AOR (95% CI)[a]	*P* value	AOR (95% CI)[a]	*P* value[a]
Overweight	0.7 (0.6, 1.0)	.03	0.9 (0.6, 1.3)	.42	0.5 (0.4, 0.8)	.01
Obese	0.9 (0.7, 1.2)	.66	1.2 (0.8, 1.8)	.31	0.6 (0.4, 1.0)	.04
Severity						
Severe	8.6 (6.6, 11)	<.0001	9.8 (7.2, 13.2)	<.0001	5.9 (3.7, 9.5)	<.0001
Moderate	Ref.	–	Ref.	–	Ref.	–
Self-infusion						
Yes	2.1 (1.5, 2.9)	<.0001	1.8 (1.2, 2.9)	.008	2.7 (1.7, 4.2)	<.0001
No	Ref.	–	Ref.	–	Ref.	–
Census Bureau Regions.						
Midwest	0.8 (0.6, 1.0)	.08	0.9 (0.6, 1.3)	.51	0.6 (0.4, 1.0)	.05
Northeast	1.0 (0.7, 1.4)	.91	1.1 (0.7, 1.7)	.72	1.0 (0.6, 1.7)	.97
South	0.8 (0.6, 1.1)	.19	0.9 (0.6, 1.3)	.54	0.8 (0.4, 1.3)	.33
West	Ref.	–	Ref.	–	Ref.	–

[a]AOR (95% CI), adjusted odds ratio (95% confidence interval) and *P* value were calculated using multiple logistic regression.